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Multiple endocrine neoplasia type 2 with malignant pheochromocytoma —Long term follow-up of a case by ^{131}I-meta-iodobenzylguanidine scintigraphy—

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The case of a 33-year-old Japanese man, who has Multiple Endocrine Neoplasia Type 2 (MEN IIa) (Sipple's syndrome) with malignant pheochromocytoma, is reported. He had survived for twelve years since the initial diagnosis of malignant pheochromocytoma. Within this period, he had undergone ^{131}I-meta-iodobenzylguanidine scintigraphy twice, in 1983 and 1990. This is the first case in Japan of a longterm surviving patient with malignant pheochromocytoma followed up by ^{131}I-MIBG scintigraphy. Although he had no exacerbation of clinical symptoms or urinary catecholamine levels, second scintigraphy clearly showed an increase in the tumor size, new metastasis of the malignant pheochromocytoma and exacerbation of the medullary thyroid carcinoma. Compared with any other roentgenological device and hormonal data, ^{131}I-MIBG scintigraphy was seen to be a good tool for evaluating the localization and the progression of tumors. ^{131}I-MIBG scintigraphy is a useful procedure not only for initial diagnosis but also for judging progression in a case of advanced malignant pheochromocytoma.

Key words: malignant pheochromocytoma, ^{131}I-MIBG, MEN type IIa, long term survival

INTRODUCTION

MALIGNANT PHEOCHROMOCYTOMA is a rare disease and the clinical manifestations are highly varied.[1–3] Although a diagnosis of pheochromocytoma can now readily be made on the basis of plasma and urinary catecholamine measurements,[4,5] pinpointing the tumor location, especially in extraadrenal cases, is often difficult and uncertain despite the availability of computed tomography (CT)[6,7] and magnetic resonance imaging. Adrenal lesions less than 2 cm in diameter and some extra-adrenal lesions considerably larger than 2 cm in diameter are frequently not visualized by CT.[6,7] Furthermore, it is difficult to detect new metastatic lesions.

The development of the guanethidine analog iodine-131 metaiodobenzylguanidine (^{131}I-MIBG), has provided a safe, specific, and non-invasive technique for diagnosis and treatment of pheochromocytoma.[8–11] We have already reported the results of the initial study of ^{131}I-MIBG scintigraphy in Japan and suggested that ^{131}I-MIBG scintigraphy appears to be useful for the diagnosis of malignant pheochromocytoma.[12] It is, however, not yet useful for evaluating the progression of the tumors and for searching of new metastasis. We report here a repeated ^{131}I-MIBG study of a long surviving patient

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with MEN IIa (Sipple's syndrome) with malignant pheochromocytoma.

CASE REPORT

A 33-year-old Japanese man was admitted to Nagasaki University Hospital for further evaluation and treatment of MEN IIa with malignant pheochromocytoma by a second ^{131}I-MIBG scintigraphy in November, 1990. There was no history of this disease in the family. He was in a normal state of health until 1979, when a paroxysmal headache and palpitation developed. At that time he was noted to have paroxysmal hypertension and greatly increased urinary catecholamines (norepinephrine (NE) 2429 μg/day and epinephrine (E) 71 μg/day: normal; 25–120 μg/day and 2–30 μg/day, respectively). Pneumoretroperitoneum and arteriogram revealed a left adrenal tumor. A left adrenal pheochromocytoma was diagnosed and the tumor on his left kidney was removed in February, 1980. Postoperatively, the patient still had paroxysmal hypertension with a continued increase in urinary catecholamines. A thyroid nodule and high serum calcitonin were also

Table 1 Endocrinological data: Plasma and urinary catecholamine levels in patient

	Normal range	1981. 9	1990. 11
Plasma epinephrine	<120 pg/ml	less than 120	1910
norepinephrine	100–410 pg/ml	5790	5330
Urinary epinephrine	2–30 μg/day	70.9	233.5
norepinephrine	25–120 μg/day	2429.0	541.1
3-methoxy-4-hydroxy mandelic acid (VMA)	1.5–6.5 mg/day	92.0	50.2
Serum calcitonin	<100 pg/ml	947	1000
CEA*	<3.0 ng/ml	4.3	20.9

*CEA RIA kit Daiichi II (Daiichi Radioisotope Lab., Ltd.)

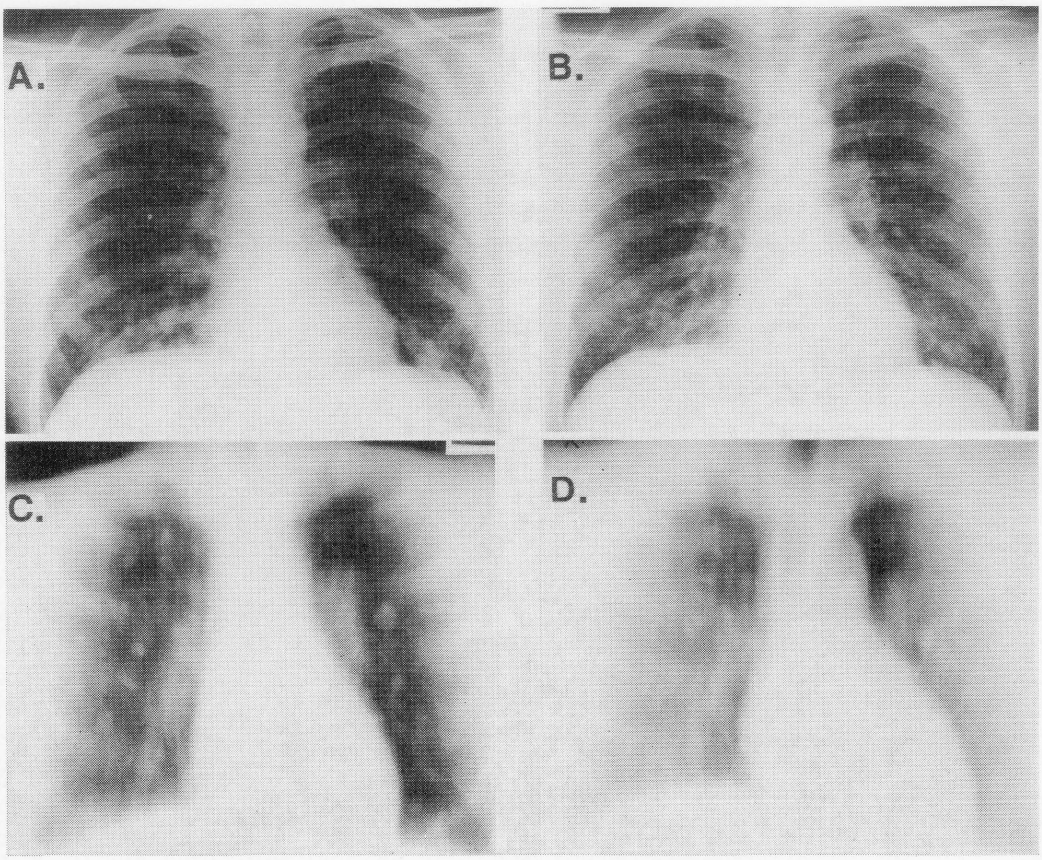

Fig. 1 The chest X-ray film (A, B) and tomography (C, D) of the patient. Left (A, C); the X-rays were taken in 1983. Right (B, D); the films were taken in 1990. Multiple metastatic lesions are seen in the field of both lungs.

noted at that time. Since histological examination at biopsy revealed that the thyroid tumor was medullary carcinoma, a diagnosis of Multiple Endocrine Neoplasia type IIa (MEN IIa) with malignant pheochromocytoma was made. The patient was referred to Nagasaki University Hospital for examination of a malignant pheochromocytoma by ^{131}I-MIBG scintigraphy first in February, 1983. ^{131}I-MIBG scintigram showed multiple metastasis of tumors to the lungs and the liver. The patient was then given propranolol 15 mg/day and prazosin 3 mg/day to effectively control his blood pressure, and he was without symptoms for the next seven years. In 1990, to further evaluate progression of the malignant pheochromocytoma, he was again admitted to our department, although he had not complained of any symptoms.

On physical examination the patient looked healthy. Blood pressure and pulse rate were found to be normal when measured repeatedly. Routine laboratory test revealed renal dysfunction. Serum BUN was 38 mg/d*l* and creatinine 4.3 mg/d*l*. Creatinine clearance was 15.6 m*l*/min. Serum total cholesterol was 263 mg/d*l*. Endocrinological laboratory data revealed increased excretion of catecholamines and metabolites (Table 1). Compared with the data in 1983, urinary norepinephrine had decreased but urinary epinephrine and serum CEA had increased. These findings suggested that the pheochromocytoma might be undifferentiated, and the medullary thyroid carcinoma was gradually exacerbated. On roentgenological examination, of the chest, multiple small metastatic tumors were seen in both lungs (Fig. 1, A, B). It was unclear whether the number and the size of the tumor had increased or not. And chest tomography failed to reveal the occurrence of new metastasis (Fig. 1, C, D). CT of the chest showed an increase in the number and size of the small nodules (Fig. 2A, B). CT of the abdomen revealed a new large tumor in the lower lobe of the liver (Fig. 2, C, D). Scintigraphy was done 24 hrs after the intravenous administration of 20 MBq (0.5 mCi) of ^{131}I-MIBG in 1983 and 1990. Thyroid uptake of ^{131}I liberated from ^{131}I-MIBG was prevented by the use of Lugol's solution, 30 mg/day, beginning on the seventh day prior to injection and continued throughout the imaging interval. ^{131}I-MIBG scintigram was able to show abnormal uptake in malignant pheochromocytomas in the whole body. Compared with the images in 1983, the images in 1990 showed abnormal accumulation in the neck, which corresponded to thyroid medullary carcinoma. (Fig. 3A, B). Increased abnormal accumulation of radioactivity in the lungs and the liver was noticed (Fig. 3C, D, E, F). These

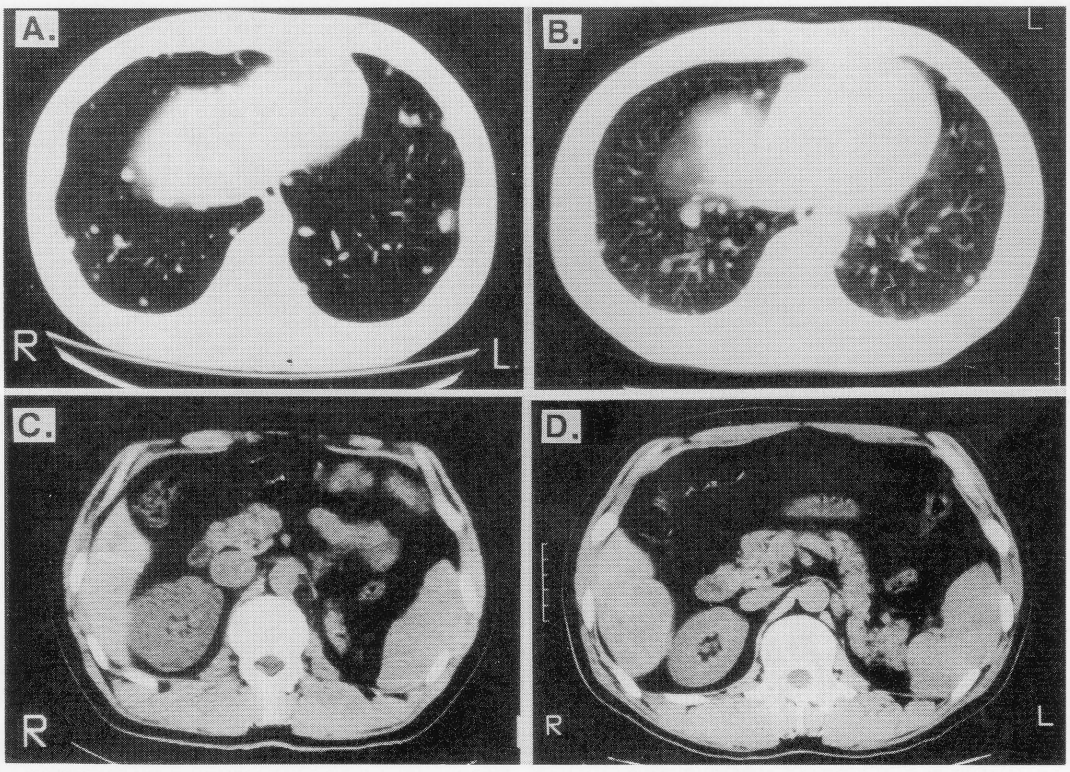

Fig. 2 The computed tomography of the chest (A, B) and the abdomen (C, D). Left (A, C); the CT scans were taken in 1983. Right (B, D); the CT scans were taken in 1990. Multiple metastatic lesions in lung are shown. The size of the tumor in liver increases.

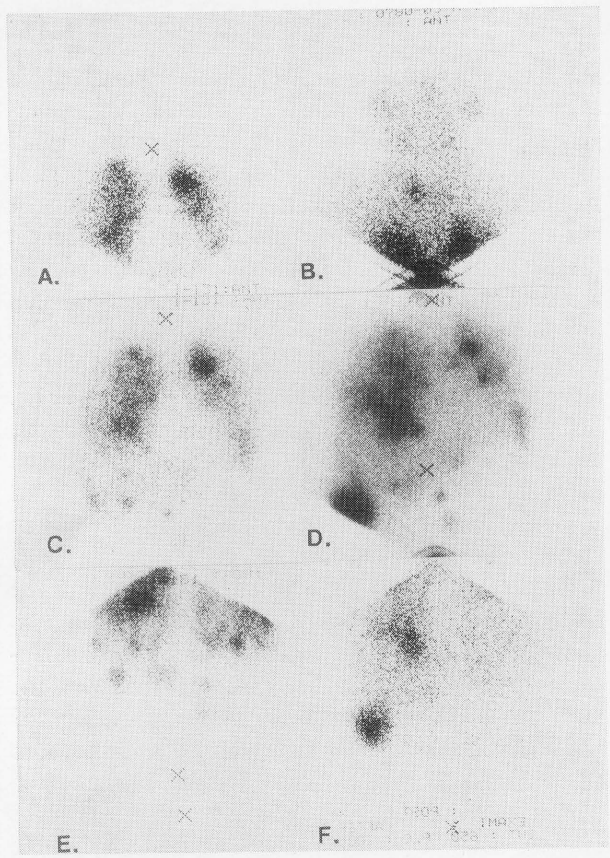

Fig. 3 ^{131}I-MIBG scintigram. Left (A, C, E); the scintigrams were taken in 1983. Right (B, D, F); the scintigrams were taken in 1990. Abnormal accumulations are observed in the lung and the liver. In 1990, new abnormal uptake lesions of thyroid was noticed. The size of tumor in liver increased, that correlated the tumor by the CT scan.

abnormalities corresponded to the metastasis of pheochromocytomas that were well correlated with the localization of tumors detected by CT. In 1990, after scintigraphy, a therapeutic dose of ^{131}I-MIBG (3.3 GBq) was administrated by slow i.v. infusion for the purpose of destroying the ^{131}I accumulated tumors. Ten months after the second ^{131}I-MIBG, the patient was still fine despite the apparent presence of these tumors.

COMMENT

The reported incidence of malignancy in pheochromocytomas varies from 10% to 32% in reports in the literature.[13,14] A malignant state can be positively diagnosed only when metastasis occurs, most often to regional lymph nodes, liver, lungs, and bones, because the usual histologic criteria of malignancy are of no aid in establishing the diagnosis.[15] The diagnosis and localization of a malignant lesion are often difficult. As our case shows, symptoms, signs and plasma and urinary catecholamines do not correlate with size, distribution, and location of the tumor.[13] Hormonal data are therefore not useful for the evaluation of progression of the tumor.

Sisson et al in 1981 first reported uptake of a new radiopharmaceutical agent, ^{131}I-MIBG, in both benign and malignant pheochromocytomas.[8] ^{131}I-MIBG scintigraphy has proven to be a reliable means of localizing pheochromolcytoma.[12] For the detection of extra-adrenal or malignant pheochromocytoma and postoperative recurrence of pheochromocytoma, ^{131}I-MIBG-scintigraphy is superior to CT.[16] Also, for some malignant metastatic diseases, ^{131}I-MIBG scintigraphy has proven to be more sensitive than conventional X-ray or other scintigraphic procedure.[17] The sensitivity of diagnostic ^{131}I-MIBG scintigraphy for pheochromocytoma is 87–91%; the specificity is 94–99%.[11] Using ^{131}I-MIBG scintigraphy, Beierwaltes et al found metastasis of a malignant pheochromocytoma in 46% of their cases compared to some 10% observed with conventional diagnostic methods.[18] The accumulation of ^{131}I-MIBG is also demonstrated in neuroblastoma and medullary carcinoma of the thyroid gland.[12]

Although the spontaneous clinical course of malignant pheochromocytoma can greatly vary from rapidly progressive to almost stationary, the 5-year survival rate averaged about 40%.[13,16] Recently, newly improved antihypertensive drugs, alpha and beta blockade, prevent life-threatening cardiovascular involvements and permit prolonged survival and good quality of life despite widely disseminated tumors.[17] The number of long-survival cases is indeed increasing.[19] Lifetime follow-up is mandatory because metastasis or recurrence of pheochromocytoma may occur up to 20 years after initial surgery.[14,16]

In our case, the progression of tumor size, the occurrence of new metastasis of the pheochromocytoma and the exacerbation of the medullary thyroid carcinoma were clearly detected after a seven year follow-up period. CT and angiography may provide better anatomical resolution but are not well suited for screening the entire body and might be reserved for confirmation and detailed delineation of anatomical relations in cases with a positive scan.[21] ^{131}I-MIBG scintigraphy is a good procedure for following up the progression of malignant pheochromocytoma.

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